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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/477,147	06/07/95	LIVINGSTON P	43016-D/JPW/

HM12/0411

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EXAMINER	
DUFFY,P	
ART UNIT	**PAPER NUMBER**
1645	20

DATE MAILED: 04/11/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	08/477,147	Livingston et al.
	Examiner	Group Art Unit
	Duffy	1645

☒ Responsive to communication(s) filed on 129(a) and amendment filed 1/24/98.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 57-101 is/are pending in the application.

Of the above, claim(s) 57-70 and 98-101 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 71-97 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 57-101 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 1-24-00 has been entered.

2. The amendment filed 1-24-2000 has been entered into the record. Claims 57-101 are now pending.

3. The previously submitted composition claims 57-70 and newly submitted claims 98-101 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the compositions as claimed are distinct because they can be used in a materially different process such as linked to a column for purification of cross reactive antibodies, in an *in vitro* method to study immune responses or in an *in vitro* method to generate monoclonal antibodies.

Since applicant has received an action on the merits for ***the originally presented methods*** invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57-70 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicants assert that the claims do not define patentably distinct inventions and the Groups should be rejoined. Applicants remarks are not persuasive because the compositions can be used in materially different methods and are *distinct as set forth above (MPEP 806.05(h))*, the restriction is proper and is made final. In the instant case the inventions are related as

disclosed but distinct as claimed, restriction is proper. There is no requirement that the inventions be both independent and distinct as asserted by applicants. Applicants are directed to MPEP, Seventh Edition, July 1998, page 800-3, section 803 "(A) the inventions must be independent (see MPEP§ 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05 - § 806.05(I)). Moreover, there is an undue search and examination burden, since the inventions are classified differently necessitating a different search of at least the US Patents.

Additionally, applicants may not petition under 37 CFR 1.129(b) to rejoin, because no restriction has been made in the present application due to actions by the applicant, as clearly evidenced by the cancellation of compositions in preliminary amendments A, mailed 6-7-95 and B, mailed 11-15-95.

4. This application contains claims 57-70 and 98-101 drawn to an invention nonelected by original presentation.

5. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Priority

6. Applicants recently filed a request for a corrected filing receipt indicating that the instant application was a 371 of PCT/US/9400757 and a CIP of 08/009,268 filed 01/22/93, now abandoned. It is noted that the instant application 08/477,147 WAS NOT filed under 37 US 371. It is not now, nor ever has been accorded 371 status. Applicant may not retroactively convert a 35 USC 111 filing to a 35 USC 371. Correction is required in response to this office action.

Double Pat nting

7. Claims 71-97 are *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 65-71 and 77 of copending Application No. 08/477,097. Although the conflicting claims are not identical, they are not patentably distinct from each other because they all claim conjugating proteins to gangliosides through the ceramide portion and thus the particular method species drawn to GM2 or GM3 claimed in the copending application would anticipate the instant genus method claims. Applicants' argue that the provisional rejection should be allowed to drop and that the instant claims be allowed to issue, pursuant to MPEP section 804. Since the instant claims are not allowable, the provisional double patenting rejection is maintained for reasons already made of record.

8. Claims 71-97 are *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 66-72 of copending Application No. 08/475,784. Although the conflicting claims are not identical, they are not patentably distinct from each other because they all claim conjugating proteins to gangliosides through the ceramide portion and thus the particular method species claimed in the copending application would anticipate the instant genus method claims.

Applicants' argue that the provisional rejection should be allowed to drop and that the instant claims be allowed to issue, pursuant to MPEP section 804. Since the instant claims are not allowable, the provisional double patenting rejection is maintained for reasons already made of record.

9. Claims 71-97 are *provisionally* rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 80-86 and 92-96 of copending Application No. 08/196,154. Although the conflicting claims are not identical, they are

not patentably distinct from each other because they all claim conjugating proteins to gangliosides through the ceramide portion and thus the particular method species claimed in the copending application would anticipate the instant genus method claims.

Applicants argue that the provisional rejection should be allowed to drop and that the instant claims be allowed to issue, pursuant to MPEP section 804. Since the instant claims are not allowable, the provisional double patenting rejection is maintained for reasons already made of record.

Claim Rejections - 35 USC § 112

10. Claims 71-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons made of record for claims 44 and 46-56 in Paper No. 13, mailed 4-1-98 and reasons herein.

As to claims 72-77 and 89-97, Applicants arguments and evidence has been carefully evaluated but is not persuasive to remove the rejections of record in regard to prevention of cancer, and prevention of relapse of cancer. Applicants provide Zhong et al (Cancer Research, 58:2844-2849, 1998) and contend that Zhong et al protects against syngeneic tumor challenge and eliminates micro metastases. This evidence is not persuasive for instant prevention of cancer or prevention of relapses for the reasons set forth below. First, the composition did not prevent cancer as is claimed (see claims 72 and dependent claims). As seen on page 2846, while the composition comprising GD2 conjugated to KLH via the ceramide double bond to aldehyde by ozonolysis and attachment of KLH by reductive amination in the presence of

cyanoborohydride in combination with QS-21 extended survival, however, mice still died. Prevention of cancer is not still enabled even with the composition comprising GD2 conjugated to KLH via the ceramide double bond to aldehyde by ozonolysis and attachment of KLH by reductive amination in the presence of cyanoborohydride in combination with QS-21. In regard to prevention, the tumor challenge was limited to a single type of cancer and administered by intravenous challenge. The claims are broadly drawn to prevention of any cancer and is not limited to the specific conjugate and lymphoma treated. In contrast to solid tumors, the intravenous compartment would be expected to have any antibodies present in high concentration. This situation is unlike the majority of cancers which are not present in the intravenous compartment. Applicants have not provided evidence that solid tumors can be either treated or prevented by administration of any compositions as is claimed. Curti et al (Critical Reviews in Oncology/Hematology, 14:29-39, 1993) teach the numerous physical barriers to drug delivery in solid tumors. Applicants have not taught these types of cancers can be prevented prior to the onset of cancer or any relapses also prevented. Zhong et al teach that the administration of the composition after a reduced tumor challenge did not provide a statistically significant difference (see page 2847, column 1, second full paragraph) between the control and the composition. Thus, prevention is not enabled and relapses are not enabled since the Zhong et al article does not address this issue. The elimination of growth of micrometastices over a short time period does not enable prevention of relapses, because the primary tumor is still present and relapses can occur at the primary tumor site. All relapses are not due to metastacies. Thus, the specification as originally filed does not enable the prevention of any type of cancer.

As to claims 71-97, the claims are still not enabled for derivatives of KLH wherein the derivative is comprises KLH linked to an immunological adjuvant. The specification does not teach how to link or conjugate immunological adjuvants, such as cytokines, non-ionic block copolymer or monophospholipid A, to the KLH moiety. The specification does not teach that the compositions so made function to boost the immune response toward the oligosaccharide moiety, rather than the KLH moiety to which the adjuvant is attached or are useful in any manner contemplated by the specification. The specification does not reference any art accepted method of making said derivatives. Pierce (U.S. Patent No. 5,616,477) teaches that many materials have been shown to have adjuvant activity , however such chemical coupling involves harsh treatment and often results in destruction of a portion of the antigen and reduced immunogenicity (column 1, lines 30-40). Applicants have not taught how to make a ganglioside coupled to or linked to a derivative of KLH as instantly claimed, wherein the ganglioside or oligosaccharide portion of the ganglioside retains its immunogenicity at any level, especially at that level which is required to treat or prevent cancer as is instantly claimed. Moreover, the art teaches that the antigen *per se* is directly coupled to the immunological adjuvant. The claim requires that the adjuvant be linked through the KLH carrier protein and thus the adjuvant would be expected to increase the immunogenicity of the KLH rather than the ganglioside or oligosaccharide attached thereto. In view of the absence of showing of the ability of such compositions to prevent of cancer or prevent relapses of cancer, the absence of any teaching of how to make these derivatives suitable for use in the claimed methods, one skilled in the art would be forced into undue experimentation to make such derivatives and use them in the methods of the invention as are now claimed. In the absence of further guidance on how to

make the ganglioside-KLH derivative, it would require undue experimentation to predictably and reproducibly make the compositions and use the compositions in the claimed.

The rejection is maintained.

11. Claims 71-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al (Cancer Research, 49:7045-7050, 1989) in view of Irie et al (U.S. Patent No. 4,557,931, published December 10, 1985) and Ritter et al (Cancer Biology, 2:401-409, 1991) is maintained and reiterated below.

Livingston et al (Cancer Research, 49:7045-7050, 1989) teach a composition administered to melanoma patients for stimulating the production of antibodies directed to a carbohydrate epitope on the ganglioside, GM2 (p7046-7048). Livingston et a teach that the GM2 is administered in conjunction with an adjuvant, Bacillus Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline (p 7048, column 1, paragraph 3 and paragraph bridging p 7046-47). Livingston et al teach that the melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination (p 7048 paragraph 1, and column 2, paragraph 2). Livingston et al teach that more patents produced IgM antibodies that IgG antibodies to the GM2 (p 7047 paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (p 7045, column 1, paragraph 2). Livingston et al do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH) through the ceramide portion of the ganglioside or use of any of the other gangliosides in a method to induce an immune response or cancer treatment.

Irie et al teach conjugation of ganglioside GM2 to a non-toxic protein carrier, such as albumin, using ozonolysis (column 5, see B., lines 19-68) which conjugates a the GM2 through the ceramide portion. Irie et al teach that the fatty acid of ceramide maybe removed leaving sphingosine and thus the coupling takes place through the amine group of the sphingosine moiety (column 2, lines 64-69). Irie et al teach that the conjugated GM2 can be used as a vaccine to stimulate an immune response and raise the anti-GM2 titer in mammals (column 2). Irie et al differ by not conjugating the GM2 to KLH.

Ritter et al (Cancer Biology, 2:401-409, 1991) teach that the IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (p 406, paragraph 1). Ritter et al discloses the advantage of using an IgG antibody response (versus IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediated antibody-dependent cell-mediated cytotoxicity; and d) is generally detectable in the serum for longer periods after immunization.

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the GM2-albumin ceramide conjugate of Irie et al by substituting KLH for albumin and to substitute the resulting GM2-KLH ceramide conjugate for the GM2 in the immunization composition of Livingston et al for active immunization for generating antibody response for melanoma treatment because Irie et al teach that the GM2 conjugated through the ceramide (sphingosine) portion can be used as a vaccine to simulate an immune response and raise the anti-GM2 titer in mammals and Ritter et al teach that the IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (p 406, paragraph 1) and Ritter et al discloses the advantages of

generating and IgG as opposed to an IgM antibody response and optimization of the dosage, route of administration and number of sites to administer the composition as combined above is well within the skill of the art.

Applicants allege that the references neither individually or combined teach the invention as is now claimed. This is not persuasive. Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

12. Claims 71-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

Livingston et al (Cancer Research) teach a composition administered to melanoma patients for stimulation the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (page 7046-7048). Livingston et al teach that the composition for treatment is administered at a concentrations of 100, 200, or 300 ug with an adjuvant, Bacillus-Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, (p 7046, column 1, paragraph 3, and paragraph bridging p 7046-47). Livingston et al teach that

melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). Livingston et al teach treatment of a melanoma, a cancer which is both epithelial and neuroectodermal in origin. Livingston et al differ by not teaching the conjugation of the GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on Keyhole Limpet Hemocyanin (KLH) in a composition and using this composition for treatment.

Ritter et al (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). Ritter et al teaches discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Liane et al (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group bearing glass beads.

Ritter et al (1990) teach that GD3 lactone is more immunogenic than GD3.

Livingston et al (U.S. Patent No. 5, 102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Livingston et al by conjugating the GM-2 to KLH by covalently coupling GM2 to KLH by substituting GM2 for the globoside and KLH for the aminoethyl agarose to produce a GM-2-KLH conjugate by means of the olefinic bond of the sphingosine moiety of the GM2 (i.e. the instant ceramide double bond) and the ε-aminolysyl groups present in the KLH protein using the method of Liane et al and add QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages by Ritter et al (1991) and adding the QS-21 would be advantageous because it provides for a higher antibody response that the commonly used adjuvant use by

Kensil et al and QS-21 provides the advantages that it is not toxic to animals as is taught by Marciani et al. It also would have been *prima facie* obvious to use doses of between 10 and 80 ug of QS-21 in the composition and optimize the dose accordingly because the immune response with QS-21 plateaus at doses between 10-80 ug and optimization of the weight ratio of the components of the composition to provide an optimal response is well within the ordinary skill in the art and use the composition as modified *supra* for treatment of melanoma as taught by Livingston et al (Cancer Research) . It also would have been *prima facie* obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined *supra* because they are all prominent cell-membrane components of melanomas as taught by Livingston et al (U.S. Patent No. 5,102,663) and one of ordinary skill in the art would react with the melanoma cells. It would have also been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GD3 lactone for the GM2 ganglioside in the composition because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al (1990) and would be expected to product an enhanced antibody response as compared to GD3. Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is will within the skill of the ordinary artisan. One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the ε-aminolysyl groups of carrier proteins for enhance immunogenicity is routine in the art and Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies.

New Rejections Based on Amendment

13. Claims 71-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

As to claims 71-97, Applicants point to page 32, lines 1-33 and page 12, lines 4-14 for support for the now claimed invention. This is not persuasive, the passage at page 32, lines 4-14 provide for a *specific coupling procedure at the C-4 carbon of the sphingosine moiety of the ceramide to the ε-aminolysyl group of a proteins* (ozonolysis, production of a functional aldehyde group and coupling to an ε-aminolysyl group on a protein by reductive amination). The passage at page 12, lines 4-14 in combination with the passage at page 32, lines 1-33 does not support a broad coupling to any generic portion of the ceramide backbone of the ganglioside, by any generic means by cleavage of any double bond (i.e. C=O) and coupling by any linkage process. The written description at pages 12 and 32 does not support by way of written description, convey that applicants had at the time of filing contemplated any means of coupling to any carbon portion of the ceramide, a concept that is now broadly claimed. Applicants were clearly not in possession of that which is now broadly claimed. Correction is required.

As to claims 89-97, the concept of using the composition for preventing a relapse of cancer in a subject comprising administering the composition is not found in either the detailed description of the invention at pages 11-18, nor at the indicated pages of 12, 32, 33, 76, 114 or 116 of the specification as alleged by applicants. This issue is best resolved by applicants pointing to the specificaiton by page and line number where written description support for conception of this now claimed invention can be found.

Status of Claims

14. All claims stand rejected.

Conclusion

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
April 7, 2000

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600